WHAT IS CLAIMED IS:

1. A modified cytokine that exhibits increased resistance to proteolysis compared to the unmodified cytokine or a modified cytokine selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID Nos. 2-181, 233-1303 or a structural homolog thereof.

2. The modified cytokine of claim 1, selected from the group consisting of a member of the interferons/interleukin-10 protein family, a member of the long-chain cytokine family and a member of the short-chain cytokine family, wherein the modified cytokine is a modified interferon α of any of SEQ ID Nos. 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987 or a cytokine modified on the basis of 3-dimensional structural homology with any of SEQ ID Nos. 87, 89, 90, 93, 96, 101, 103, 107, 124, 979, 980, 983, 984, 985, 986 and 987.

3. The modified cytokine of claim 1 selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha-2a (IFNα-2a), interferon alpha-2b (IFNα-2b), and interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

4. The modified cytokine of claim 1, that is an interferon.

5. The modified cytokine of claim 1, that is an interferon α-2b (IFNα-2b), interferon α-2a (IFNα-2a), interferon α-2c (IFNα-2c) or an interferon having the sequence set forth in SEQ ID No. 232.

6. A modified cytokine of claim 4, that is IFNα-2b or IFNα-2a or IFNα-2C selected from the group consisting of proteins comprising one or

more single amino acid replacements in SEQ ID No. 1 or 182, corresponding to the replacement of: L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165,

wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

7. The modified cytokine of claim 6, wherein:

the protein is human;

has more resistance to proteolysis than the unmodified protein; and

the protein is selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:1 or 182, corresponding to: F by V at position 27; R by H at position 33; E by Q at position 41; E by H at position 41; E by Q at position 58; E by H at position 58; E by Q at position 78; E by H at position 78; Y by H at position 89; E by Q at position 107; E by H at position 107; P by A at position 109; L by V at position 110; M by V at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; K by Q at position 133; K by T at position 133; E by Q at position 159 and E by H at position 159.

8. A modified IFNα-2b or IFNα-2a cytokine of claim 5 selected from the group consisting of proteins comprising one or more sets of dual-amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:

D by N at position 2 and P by S at position 4;

D by N at position 2 and P by T at position 4;

L by N at position 3 and Q by S at position 5;

L by N at position 3 and Q by T at position 5;

P by N at position 4 and T by S at position 6;

P by N at position 4 and T by T at position 6;

Q by N at position 5 and H by S at position 7;

Q by N at position 5 and H by T at position 7;

T by N at position 6 and S by S at position 8;

T by N at position 6 and S by T at position 8;

H by N at position 7 and L by S at position 9;

H by N at position 7 and L by T at position 9;

S by N at position 8 and G by S at position 10;
S by N at position 8 and G by T at position 10;
L by N at position 9 and S by S at position 11;
L by N at position 9 and S by T at position 11;
M by N at position 21 and K by S at position 23;
M by N at position 21 and K by T at position 23;
R by N at position 22 and I by S at position 24;
R by N at position 22 and I by T at position 24;
R or K by N at position 23 and S by S at position 25;
R or K by N at position 23 and S by T at position 25;
I by N at position 24 and L by S at position 26;
I by N at position 24 and L by T at position 26;
S by N at position 25 and F by S at position 27;
S by N at position 25 and F by T at position 27;
L by N at position 26 and S by S at position 28;
L by N at position 26 and S by T at position 28;
S by N at position 28 and L by S at position 30;
S by N at position 28 and L by T at position 30;
L by N at position 30 and D by S at position 32;
L by N at position 30 and D by T at position 32;
K by N at position 31 and R by S at position 33;
K by N at position 31 and R by T at position 33;
D by N at position 32 and H by S at position 34;
D by N at position 32 and H by T at position 34;
R by N at position 33 and D by S at position 35;
R by N at position 33 and D by T at position 35;
H by N at position 34 and F by S at position 36;
H by N at position 34 and F by T at position 36;
D by N at position 35 and G by S at position 37;
D by N at position 35 and G by T at position 37;
F by N at position 36 and F by S at position 38;

F by N at position 36 and F by T at position 38;
G by N at position 37 and P by S at position 39;
G by N at position 37 and P by T at position 39;
F by N at position 38 and Q by S at position 40;
F by N at position 38 and Q by T at position 40;
P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
E by N at position 42 and G by S at position 44;
E by N at position 42 and G by T at position 44;
F by N at position 43 and N by S at position 45;
F by N at position 43 and N by T at position 45;
G by N at position 44 and Q by S at position 46;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;
N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;
Q by N at position 46 and Q by T at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
Q by N at position 48 and A by S at position 50;
Q by N at position 48 and A by T at position 50;
K by N at position 49 and E by S at position 51;
K by N at position 49 and E by T at position 51;
A by N at position 50 and T by S at position 52;
A by N at position 50 and T by T at position 52;
S by N at position 68 and K by S at position 70;
S by N at position 68 and K by T at position 70;

K by N at position 70 and S by S at position 72;
K by N at position 70 and S by T at position 72;
A by N at position 75 and D by S at position 77;
A by N at position 75 and D by T at position 77;
D by N at position 77 and T by S at position 79;
D by N at position 77 and T by T at position 79;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
Q by N at position 101 and V by S at position 103;
Q by N at position 101 and V by T at position 103;
G by N at position 102 and G by S at position 104;
G by N at position 102 and G by T at position 104;
V by N at position 103 and V by S at position 105;
V by N at position 103 and V by T at position 105;
G by N at position 104 and T by S at position 106;
G by N at position 104 and T by T at position 106;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
T by N at position 108 and I by S at position 110;
T by N at position 108 and I by T at position 110;
K by N at position 134 and S by S at position 136;
K by N at position 134 and S by T at position 136;
S by N at position 154 and N by S at position 156;
S by N at position 154 and N by T at position 156;
T by N at position 155 and L by S at position 157;
T by N at position 155 and L by T at position 157;
N by N at position 156 and Q by S at position 158;

N by N at position 156 and Q by T at position 158;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
Q by N at position 158 and S by S at position 160;
Q by N at position 158 and S by T at position 160;
E by N at position 159 and L by S at position 161;
E by N at position 159 and L by T at position 161;
S by N at position 160 and R by S at position 162;
S by N at position 160 and R by T at position 162;
L by N at position 161 and S by S at position 163;
L by N at position 161 and S by T at position 163;
R by N at position 162 and K by S at position 164;
R by N at position 162 and K by T at position 164;
S by N at position 163 and E by S at position 165; and
S by N at position 163 and E by T at position 165,

wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

9. A modified IFNα-2b or IFNα-2a mutant cytokine of claim 5 selected from the group consisting of proteins comprising one or more sets of dual amino acid replacements in SEQ ID NOS:1 or 182, corresponding to:

Q by N at position 5 and H by S at position 7;
P by N at position 39 and E by S at position 41;
P by N at position 39 and E by T at position 41;
Q by N at position 40 and E by S at position 42;
Q by N at position 40 and E by T at position 42;
E by N at position 41 and F by S at position 43;
E by N at position 41 and F by T at position 43;
F by N at position 43 and N by S at position 45;
G by N at position 44 and Q by T at position 46;
N by N at position 45 and F by S at position 47;

N by N at position 45 and F by T at position 47;
Q by N at position 46 and Q by S at position 48;
F by N at position 47 and K by S at position 49;
F by N at position 47 and K by T at position 49;
I by N at position 100 and G by S at position 102;
I by N at position 100 and G by T at position 102;
V by N at position 105 and E by S at position 107;
V by N at position 105 and E by T at position 107;
T by N at position 106 and T by S at position 108;
T by N at position 106 and T by T at position 108;
E by N at position 107 and P by S at position 109;
E by N at position 107 and P by T at position 109;
L by N at position 157 and E by S at position 159;
L by N at position 157 and E by T at position 159;
E by N at position 159 and L by S at position 161; and
E by N at position 159 and L by T at position 161.

10. A modified cytokine of claim 5, further comprising one or more pseudo-wild type mutations.

11. The modified cytokine of claim 10 that is IFNα-2b or IFNα-2a.

12. A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b or IFNα-2a corresponding to SEQ ID NOS:1 or 182, amino acid residues: 9, 10, 17, 20, 24, 25, 35, 37, 41, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 89, and 90, wherein the mutations are selected from the group consisting of one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a protein set forth in SEQ ID NOS:1 or 182.

13. A modified IFNα-2b or IFNα-2a cytokine of claim 11, comprising one wherein the pseudo-wild type replacements are one or more mutations in SEQ ID No. 1 or 182 corresponding to:

P by A at position 4; Q by A at position 5,
T by A at position 6; L by A at position 9,
LG by A at position 10; L by A at position 17,
Q by A at position 20; I by A at position 24,
S by A at position 25; D by A at position 35,
G by A at position 37; G by A at position 39;
E by A at position 41; E by A at position 42
E by A at position 51; T by A at position 52,
P by A at position 54; V by A at position 55
L by A at position 56; H by A at position 57,
E by A at position 58; I by A at position 60,
I by A at position 63; F by A at position 64,
N by A at position 65; W by A at position 76,
D by A at position 77; E by A at position 78
L by A at position 81; Y by A at position 85
Y by A at position 89; Q by A at position 90
G by A at position 104; L by A at position 110
S by A at position 115 and E by A at position 146.

14. A modified cytokine of claim 5, comprising one or more pseudo-wild type mutations at amino acid positions of IFNα-2b, IFNα-2c or a protein having the sequence set forth in SEQ ID No. 232 corresponding amino acid residues: 4, 5, 6, 9, 10, 17, 20, 24, 25, 35, 37, 39, 41, 42, 51, 52, 54, 56, 57, 58, 60, 63, 64, 65, 76, 77, 78, 81, 85, 89, 90, 104, 110, 115 and 146 to SEQ ID No. 1, 182 or 232, wherein the mutations are selected from the group consisting of one or more of insertions, deletions and replacements of the native amino acid residue(s), wherein residue 1 corresponds to residue 1 of the mature interferon set forth in SEQ ID No.1, 182 or 232.

15. The modified cytokin of claim 14, wherein the pseudowild type replacements are one or more mutations selected from:

P by A at position 4; Q by A at position 5;

T by A at position 6; L by A at position 9;

LG by A at position 10; L by A at position 17;

Q by A at position 20; I by A at position 24;

S by A at position 25; D by A at position 35;

G by A at position 37; G by A at position 39;

E by A at position 41; E by A at position 42;

E by A at position 51; T by A at position 52;

P by A at position 54; V by A at position 55;

L by A at position 56; H by A at position 57;

E by A at position 58; I by A at position 60;

I by A at position 63; F by A at position 64;

N by A at position 65; W by A at position 76;

D by A at position 77; E by A at position 78;

L by A at position 81; Y by A at position 85;

Y by A at position 89, Q by A at position 90;

G by A at position 104; L by A at position 110;

S by A at position 115 and E by A at position 146, wherein the positions correspond to SEQ ID No. 1, 182, 185 or 232.

16. A modified cytokine of claim 5 that has increased antiviral activity compared to the unmodified cytokine.

17. The modified cytokine of claim 16, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR).

18. A modified cytokine of claim 5 that has more antiviral activity than antiproliferative activity compared to the unmodified cytokine.

19. The modified cytokine of claim 18, wherein antiproliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

20. A modified cytokine of claim 5 that that binds to an IFN receptor, but exhibits decreased antiviral activity and decreased antiproliferative activity relative to its receptor binding activity when compared to the unmodified cytokine.

21. A modified cytokine of claim 1, comprising two or more mutations.

22. The modified cytokine of claim 21 that is a modified IFNα-2b cytokine.

23. A modified cytokine of claim 1, wherein the cytokine comprises the sequence of amino acids set forth in any of SEQ ID Nos 2 through 181, wherein the arginine at position 23 is replaced with a lysine.

24. A modified cytokine of any claim 1 selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

25. A collection of the modified cytokines of claim 1, wherein the modified cytokines contain one or a plurality of mutations.

26. A nucleic acid molecule encoding a modified cytokine of claim 1.

27. A vector comprising a nucleic acid molecule of claim 26.

28. A eukaryotic cell, comprising the vector of claim 27.

29. A collection of nucleic acid molecules comprising a plurality of the molecules of claim 26.

30. A collection of nucleic acid molecules comprising a plurality of the vectors of claim 27.

31. A method for expression of a modified cytokine, comprising:

introducing a nucleic acid of claim 26 into a host; and

culturing the cell, under conditions and in which the modified encoded cytokines are expressed.

32. The method of claim 31, wherein the nucleic acid is introduced into a host cell.

33. The method of claim 31, wherein the cytokine is a modified IFNα-2b, IFNα-2a cytokine IFNα-2c or interferon of SEQ ID No. 232.

34. The method of claim 31, wherein the host is a eukaryotic host cell.

35. The method of claim 34, wherein the cytokine is glycosylated.

36. The method of claim 31, wherein expression is effected *in vivo*.

37. The method of claim 31, wherein expression is effected *in vitro*.

38. The method of claim 31, wherein expression is effected in a cell-free system.

39. A modified cytokine claim 2, comprising two or more mutations.

40. A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

41. A modified cytokine of claim 5 that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNα-2b or IFNα-2a or IFNα-2c or consensus IFNα of SEQ ID No. 232.

42. A modified cytokine of claim 41, wherein the resistance to proteolysis is measured by mixing it with a protease in vitro, incubation with blood or incubation with serum.

43. A modified cytokine of claim 1 that is a structural homolog of IFNα-2b, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFNα-2b or IFNα-2a or IFNα 2c or an interferon of SEQ ID No. 232.

44. A modified cytokine of claim 43, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood or incubation with serum.

45. The cytokine of claim 44 that is an IFNα cytokine.

46. The cytokine of claim 45, selected from the group consisting of IFNα-2a, IFNα-c, IFNα-2c, IFNα-d, IFNα-5, IFNα-6, IFNα-4, IFNα-4b, IFNα-I, IFNα-J, IFNα-H, IFNα-F, IFNα-8, and IFNα-consensus cytokine.

47. A modified cytokine of claim 1 that is modified IFNα-2a cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO. 182 in the IFNα-2a corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of unmodified IFNα-2b, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-2a.

48. The modified IFNα-2a of claim 47, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 182, corresponding to amino acid positions 41, 58, 78, 107, 117, 125, 133 and 159.

49. A modified IFNα-c cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO. 183 in

the IFNα-c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFN alpha-c.

50. The modified IFNα-c of claim 49, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 183, corresponding to amino acid positions 41, 59, 79, 108, 118, 126, 134 and 160.

51. A modified IFNα-c, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 185 in the IFNα-2c corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-2c.

52. The modified IFNα-2c cytokine of claim 51, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 185, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

53. A modified IFNα-d cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 186 in the IFNα-d corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-d.

54. The IFNα-d modified cytokine of claim 53, that is human and is selected from the group consisting of cytokines comprising one or more

single amino acid replacements in SEQ ID NO: 186, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

55. A modified IFNα-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 187 in the IFNα-5 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-5.

56. The IFNα-5 modified cytokine of claim 55, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 187, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

57. A modified IFNα-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 188 in the IFNα-6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-6.

58. The IFNα-6 modified cytokine of claim 57, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 188, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

59. A modified IFNα-4 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 189 in the IFNα-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines

of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4.

60. The IFNα-4 modified cytokine of claim 59, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 189, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

61. A modified IFNα-4b cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 190 in the IFNα-4b corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-4b.

62. The IFNα-4b modified cytokine of claim 61, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 190, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111, 112, 114, 118, 122, 126, 134 and 160.

63. A modified IFNα-I cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 191 in the IFNα-I corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-I.

64. The IFNα-I modified cytokine of claim 63, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 191, corresponding to

amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

65. A modified IFNα-J cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 192 in the IFNα-J corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-J.

66. The IFNα-J modified cytokine of claim 65, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 192, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

67. A modified IFNα-H cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 193 in the IFNα-H corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-H.

68. The IFNα-H modified cytokine of claim 67, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 193, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

69. An IFNα-F cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 194 in the IFNα-F corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as

assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-F.

70. The IFNα-F modified cytokine of claim 69, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 194, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

71. An IFNα-8 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 195 in the IFNα-8 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-8.

72. The IFNα-8 modified cytokine of claim 71, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ ID NO: 195, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

73. An IFNα-consensus cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 232 in the IFNα-consensus cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNα-consensus.

74. The modified cytokine of claim 1 that is an IFNα-consensus cytokine, that is human and is selected from the group consisting of cytokines comprising one or more single amino acid replacements in SEQ

ID NO: 232, corresponding to amino acid positions 27, 33, 41, 59, 79, 90, 108, 110, 111,112, 114, 118, 122, 126, 134 and 160.

75. A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 196 in the IFNα-β cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

76. A modified IFNβ cytokine of claim 1, comprising mutations at one or more amino acid residues of IFNβ corresponding to SEQ ID NO:196 at positions corresponding to: 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

77. The modified IFNβ cytokine of claim 75, wherein the replacements are selected from the group consisting of amino acid sustitutions in SEQ ID NO:196 corresponding to: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at

position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

78. A modified cytokine that is an IFNβ-1 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 197 in the IFNβ-1 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNβ-1.

79. A modified cytokine of claim 4 that is an IFNβ-1 cytokine, comprising mutations at one or more amino acid residues of IFNβ-1 corresponding to SEQ ID NO: 197 at positions 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

80. A modified cytokine that is an IFNβ-2a cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 198 in the IFNβ-2a corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNβ-2a.

81. A modified cytokine of claim 4 that is an IFNβ-2a cytokine, comprising mutations at one or more amino acid residues of IFNβ-2a corresponding to SEQ ID NO:198 at positions 39, 42, 45, 47, 52, 67, 71, 73, 81, 107, 108, 109, 110, 111, 113, 116, 120, 123, 124, 128, 130, 134, 136, 137, 163 and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

82. A modified IFN-gamma cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 199 in the IFN-gamma corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFN-gamma.

83. A modified cytokine of claim 4 that is an IFN-gamma cytokine, comprising mutations at one or more amino acid residues of IFN-gamma corresponding to SEQ ID NO:199 at positions 33, 37, 40, 41, 42, 58, 61, 64, 65 and 66, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).^C

84. The modified IFN-gamma cytokine of claim 82, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO:199 corresponding to:

L33V	E41Q	K58Q	D65Q
L33I	E41N	K58N	D65N
K37Q	E41H	K61Q	D66Q,
K37N	E42Q	K61N	
K40Q	E42N	K64Q	
K40N	E42H	K64N	

wherein the first amino acid listed is substituted by the second at the position indicated.

85. A modified IL-10 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 200 in the IL-10 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-10.

86. A modified IL-10 cytokine, comprising mutations at one or more amino acid residues of IL-10 corresponding to SEQ ID NO: 200 at positions 49, 50, 52, 53, 54, 55, 56, 57, 59, 60, 67, 68, 71, 72, 74, 75, 78, 81, 84, 85, 86, and 88, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

87. The modified IL-10 cytokine of claim 85, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO:200 corresponding to:

K49Q	E54N	L60V	Y72I	E81N
K49N	E54H	L60I	E74Q	E81H
E50Q	D55Q	E67Q	E74N	D84Q
E50N	D55N	E67N	E74H	D84N
E50H	F56I	E67H	E75Q	P85S
L52V	F56V	M68V	E75N	P85A
L52I	K57Q	M68I	E75H	D86Q
L53V	K57N	F71I	P78S	D86N
L53I	Y59H	F71V	P78A	K88Q
E54Q	Y59I	Y72H	E81Q	K88N,

wherein the first amino acid listed is substituted by the second at the position indicated.

88. A modified erythropoietin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 201 in the erythropoietin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified erythropoietin.

89. A modified erythropoietin of claim 88, comprising mutations at one or more amino acid residues of erythropoietin corresponding to SEQ ID NO: 201 at positions 43, 45, 48, 49, 52, 53, 55, 72, 75, 76, 123, 129, 130, 131, 162, and 165, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

90. The modified erythropoietin cytokine of claim 88, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 201 corresponding to:

D43Q	K52Q	E72N	P122S	R131H
D43N	K52N	E72H	P122A	R131Q
K45Q	R53H	L75V	D123Q	R162H
K45N	R53Q	L75I	D123N	R162Q
F48I	E55Q	R76H	P129S	D165Q
F48V	E55N	R76Q	P129A	D165N
Y49H	E55H	P121S	L130V	
Y49I	E72Q	P121A	L130I	

wherein the first amino acid listed is substituted by the second at the position indicated.

91. A modified GM-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 202 in the GM-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified GM-CSF.

92. A modified cytokine of claim 91 that is a GM-CSF cytokine, comprising mutations at one or more amino acid residues of GM-CSF corresponding to SEQ ID NO: 202 at positions 38, 41, 45, 46, 48, 49, 51, 60, 63, 67, 92, 93, 119, 120, 123, and 124, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

93. The modified GM-CSF cytokine of claim 91, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 202 corresponding to:

E38Q	D48Q	K63Q	F119V
E38N	D48N	K63N	D120Q
E38H	L49V	R67H	D120N
E41Q	L49I	R67Q	E123Q
E41N	E51Q	P92S	E123N
E41H	E51N	P92A	E123H
E45Q	E51H	E93Q	P124S
E45N	E60Q	E93N	P124A,
E45H	E60N	E93H	
M46V	E60H	F119I	
M46I			

wherein the first amino acid listed is substituted by the second at the position indicated.

94. A modified Flt3 ligand cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 203 in the Flt3 ligand corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokine of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified Flt3 ligand.

95. A modified Flt3 ligand cytokine of claim 94, comprising mutations at one or more amino acid residues of Flt3 ligand corresponding to SEQ ID NO: 203 at positions 3, 40, 42, 43, 55, 58, 59, 61, 89, 90, 91, 95, and 96, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

96. The modified Flt3 ligand cytokine of claim 94, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 203 corresponding to:

D3Q	R55Q	P89A
D3N	E58Q	P90S
D40Q	E58N	P90A
D40N	E58H	P91S
E42Q	R59H	P91A
E42N	R59Q	R95H
E42H	K61Q	R95Q
L43V	K61N	F96I
L43I	P89S	F96V,
R55H		

wherein the first amino acid listed is substituted by the second at the position indicated.

97. A modified IL-2 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 204 in the IL-2 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-2.

98. A modified IL-2 cytokine of claim 97, comprising mutations at one or more amino acid residues of IL-2 corresponding to SEQ ID NO: 204 at positions 43, 45, 48, 49, 52, 53, 60, 61, 65, 67, 68, 72, 100, 103, 104, 106, 107, 109, 110, and 132, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

99. The modified IL-2 cytokine of claim 97, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 204 corresponding to:

K43Q	L53I	E68Q	Y107I
K43N	E60Q	E68N	D109Q
Y45H	E60N	E68H	D109N
Y45I	E60H	L72V	E110Q
K48Q	E61Q	L72I	E110N
K48N	E61N	E100Q	E110H
K49Q	E61H	E100N	L132V
K49N	P65S	E100H	L132I
E52Q	P65A	F103I	E106Q
E52N	E67Q	F103V	E106N
E52H	E67N	M104V	E106H
L53V	E67H	M104I	Y107H,

wherein the first amino acid listed is substituted by the second at the position indicated.

100. A modified IL-3 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 205 in the IL-3 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-3.

101. A modified IL-3 cytokine of claim 100, comprising mutations at one or more amino acid residues of IL-3 corresponding to SEQ ID NO: 205: 37, 43, 46, 59, 63, 66, 96, 100, 101, and 103, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

102. The modified IL-3 cytokine of claim 100, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO:205 corresponding to:

F37I	E59Q	P96A
F37V	E59H	K100Q
E43Q	R63H	K100N
E43N	R63Q	D101Q
E43H	K66Q	D101N
D46Q	K66N	D103Q
D46N	P96S	D103N,

wherein the first amino acid listed is substituted by the second at the position indicated.

103. A modified SCF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 206 in the SCF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified SCF.

104. A modified SCF cytokine of claim 103, comprising mutations at one or more amino acid residues of SCF corresponding to SEQ ID NO: 206: 27, 31, 34, 37, 54, 58, 61, 62, 63, 96, 98, 99, 100, 102, 103, 106, 107, 108, 109, 134, and 137, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

105. The modified SCF cytokine of claim 103, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 206 corresponding to:

M27V	D54Q	F63I	K100Q	E106H	E134N
M27I	D54N	F63V	K100N	P107S	E134H
K31Q	D58Q	K96Q	F102I	P107A	D137Q
K31N	D58N	K96N	F102V	R108H	D137N,
P34S	D61Q	L98V	K103Q	R108Q	
P34A	D61N	L98I	K103N	L109V	
D37Q	K62Q	K99Q	E106Q	L109I	
D37N	K62N	K99N	E106N	E134Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

106. A modified IL-4 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 207 in the IL-4 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to

proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-4.

107. A modified IL-4 cytokine of claim 106, comprising mutations at one or more amino acid residues of IL-4 corresponding to SEQ ID NO: 207: 26, 37, 53, 60, 61, 64, 66, 100, 102, 103, and 126, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

108. The modified IL-4 cytokine of claim 106, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 207 corresponding to:

E26Q	E60Q	L66V	E103N
E26N	E60N	L66I	E103H
E26H	E60H	P100S	K126Q
K37Q	K61Q	P100A	K126N,
K37N	K61N	K102Q	
R53H	R64H	K102N	
R53Q	R64Q	E103Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

109. A modified IL-5 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 208 in the IL-5 cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-5.

110. A modified IL-5 cytokine of claim 109, comprising mutations at one or more amino acid residues of IL-5 corresponding to SEQ ID NO: 208 at positions 32, 34, 39, 46, 47, 56, 84, 85, 88, 89, 90, 102, 110, and 111, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

111. The modified IL-5 cytokine of claim 109, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 208 corresponding to:

R32H	E47N	E88N	E110Q
R32Q	E47H	E88H	E110N
P34S	E56Q	E89Q	E110H
P34A	E56N	E89N	W111S
K39Q	E56H	E89H	W111H,
K39N	K84Q	R90H	
E46Q	K84N	R90Q	
E46N	K85Q	E102Q	
E46H	K85N	E102N	
E47Q	E88Q	E102H	

wherein the first amino acid listed is substituted by the second at the position indicated.

112. A modified IL-13 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 209 of an IL-13 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of erythropoietin modified cytokines of claim 88, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-13.

113. A modified IL-13 cytokine of claim 112, comprising mutations at one or more amino acid residues of IL-13 corresponding to SEQ ID NO: 209 at positions 32, 34, 38, 48, 79, 82, 85, 86, 88, 107, 108, 110, and 111, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

114. The modified IL-13 cytokine of claim 112, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 209 corresponding to:

M32V	E48H	D86N	R110H
M32I	F79I	K88Q	R110Q
W34S	F79V	K88N	F111I
W34H	L82V	R107H	F111V,
L38V	L82I	R107Q	
L38I	R85H	E108Q	
E48Q	R85Q	E108N	
E48N	D86Q	E108H	

wherein the first amino acid listed is substituted by the second at the position indicated.

115. A modified G-CSF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 210 in the G-CSF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNα-2b modified cytokines of claim 5, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified G-CSF.

116. A modified G-CSF cytokine of claim 115, comprising mutations at one or more amino acid residues of G-CSF corresponding to SEQ ID NO: 210 at positions 61, 63, 68, 72, 86, 96, 100, 101, 131, 133, 135, 147, 169, 172, and 177, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

117. The modified G-CSF cytokine of claim 115, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 210 corresponding to:

W61S	F86I	E101N	F147I
W61H	F86V	E101H	F147V
P63S	E96Q	P131S	R169H
P63A	E96N	P131A	R169Q
P68S	E96H	L133V	R172H
P68A	P100S	L133I	R172Q
L72V	P100A	P135S	P177S
L72I	E101Q	P135A	P177A,

wherein the first amino acid listed is substituted by the second at the position indicated.

118. A modified leptin cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 211 in the leptin corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified leptin.

119. A modified leptin cytokine of claim 118, comprising mutations at one or more amino acid residues of leptin corresponding to SEQ ID NO: 211 at positions 43, 49, 99, 100, 104, 105, 107, 108, 141 and 142, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

120. The modified leptin cytokine of claim 118, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 211 corresponding to:

P43S	P99A	E105Q	D108N
P43A	W100S	E105N	D141Q
L49V	W100H	E105H	D141N
L49I	L104V	L107V	L142V
P99S	L104I	L107I	L142I,
		D108Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

121. A modified CNTF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 212 in the CNTF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified CNTF.

122. A modified CNTF cytokine of claim 121, comprising mutations at one or more amino acid residues of CNTF corresponding to SEQ ID NO: 212 at positions 62, 64, 66, 67, 86, 89, 92, 100, 102,

104, 131, 132, 133, 135, 136, 138, 140, 143, 148, and 151, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

123. The modified CNTF cytokine of claim 121, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 212 corresponding to:

D62Q	R89Q	E131N	E138H
D62N	E92Q	E131H	D140Q
W64S	E92N	Y132H	D140N
W64H	E92H	Y132I	P143S
E66Q	P100S	K133Q	P143A
E66N	P100A	K133N	D148Q
E66H	E102Q	P135S	D148N
L67V	E102N	P135A	L151V
L67I	E102H	R136H	L151I,
L86V	D104Q	R136Q	
L86I	D104N	E138Q	
R89H	E131Q	E138N	

wherein the first amino acid listed is substituted by the second at the position indicated.

124. A modified LIF cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 213 in the LIF corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified LIF.

125. A modified LIF cytokine of claim 124, comprising mutations at one or more amino acid residues of LIF corresponding to SEQ ID NO: 213 at positions 69, 70, 85, 99, 102, 104, 106, 109, 137, 143, 146, 148, 149, 153, 154, and 156, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

126. The modified LIF cytokine of claim 124, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 213 corresponding to:

P69S	K102N	D143Q	K153N
P69A	L104V	D143N	D154Q
F70I	L104I	Y146H	D154N
F70V	P106S	Y146I	F156I
R85H	P106A	P148S	F156V,
R85Q	L109V	P148A	
R99H	L109I	D149Q	
R99Q	Y137H	D149N	
K102Q	Y137I	K153Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

127. A modified oncostatin M cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 214 in the oncostatin M corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified oncostatin M.

128. A modified oncostatin M cytokine of claim 127, comprising mutations at one or more amino acid residues of oncostatin M corresponding to SEQ ID NO: 214 at positions 59, 60, 63, 65, 84, 87, 89, 91, 94, 97, 99, 100, 103, and 106, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

129. The modified oncostatin M cytokine of claim 127, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 214 corresponding to:

E59Q	L65I	R91Q	R100Q
E59N	R84H	K94Q	L103V
E59H	R84Q	K94N	L103I
E60Q	D87Q	D97Q	E106Q
E60N	D87N	D97N	E106N
E60H	E89Q	E99Q	E106H,
R63H	E89N	E99N	
R63Q	E89H	E99H	
L65V	R91H	R100H	

wherein the first amino acid listed is substituted by the second at the position indicated.

130. A modified IL-12 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 215 in the IL-12 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-12.

131. A modified IL-12 cytokine of claim 130, comprising mutations at one or more amino acid residues of IL-12 corresponding to SEQ ID NO: 215 at positions 56, 61, 66, 67, 68, 70, 72, 75, 78, 79, 82, 89, 92, 93, 107, 110, 111, 115, 117, 124, 125, 127, 128, 129, and 189, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

132. The modified IL-12 cytokine of claim 130, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 215 corresponding to:

K56Q	E72Q	R92H	K117Q
K56N	E72N	R92Q	K117N
E61Q	E72H	K93Q	L124V
E61N	L75V	K93N	L124I
E61H	L75I	E107Q	M125V
L66V	R78H	E107N	M125I
L66I	R78Q	E107H	P127S
E67Q	E79Q	K110Q	P127A
E67N	E79N	K110N	K128Q
E67H	E79H	M111V	K128N
L68V	F82I	M111I	R129H
L68I	F82V	E115Q	R129Q
K70Q	L89V	E115N	R189H
K70N	L89I	E115H	R189Q,

wherein the first amino acid listed is substituted by the second at the position indicated.

133. A modified hGH cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 216 in the hGH corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified hGH.

134. A modified hGH cytokine of claim 133, comprising mutations at one or more amino acid residues of hGH corresponding to SEQ ID NO: 216 at positions 56, 59, 64, 65, 66, 88, 92, 94, 101, 129, 130, 133, 134, 140, 143, 145, 146, 147, 183, and 186, wherein the mutations comprise insertions, deletions and replacements of the native amino acid residue(s).

135. The modified hGH cytokine of claim 133, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 216 corresponding to:

	E56Q	E66Q	L101V	R134Q	D147N
	E56N	E66N	L101I	K140Q	R183H
	E56H	E66H	E129Q	K140N	R183Q
	P59S	E88Q	E129N	Y143H	E186Q
5	P59A	E88N	E129H	Y143I	E186N
	R64H	E88H	D130Q	K145Q	E186H,
	R64Q	F92I	D130N	K145N	
	E65Q	F92V	P133S	F146I	
	E65N	R94H	P133A	F146V	
10	E65H	R94Q	R134H	D147Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

136. A modified IL-6 cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO: 217 in the IL-
15 6 corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of G-CSF modified cytokines of claim 115, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IL-6.

20 137. A modified IL-6 cytokine of claim 136, comprising mutations at one or more amino acid residues of IL-6 corresponding to SEQ ID NO: 217 at position 64, 65, 66, 68, 69, 75, 77, 92, 98, 103, 105, 108, 133, 138, 139, 140, 149, 156, 178, and 181, wherein the mutations comprise insertions, deletions and replacements of the native amino acid
25 residue(s).

138. The modified IL-6 cytokine of claim 136, wherein the replacements are selected from the group consisting of amino acid stitutions in SEQ ID NO: 217 corresponding to:

	P64S	F73I	R103Q	D139N
	P64A	F73V	E105Q	P140S
	K65Q	F77I	E105N	P140A
	K65N	F77V	E105H	K149Q
5	M66V	E92Q	E108Q	K149N
	M66I	E92N	E108N	W156S
	E68Q	E92H	E108H	W156H
	E68N	E98Q	D133Q	R178H
	E68H	E98N	D133N	R178Q
10	K69Q	E98H	P138S	R181H
	K69N	R103H	P138A	R181Q,
			D139Q	

wherein the first amino acid listed is substituted by the second at the position indicated.

15 139. The modified IFNα-2b cytokine of claim 5 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood 20 lysate or serum.

140. The modified IFNα-2b cytokine of claim 5 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the 25 appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

141. The modified IFNα-2b cytokine of claim 5 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in 30 the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

142. The modified IFNα-2a cytokine of claim 47 that has increased stability compared to the unmodified cytokine, wherein stability 35 is assessed by measuring residual biological activity to either inhibit viral

replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

143. The modified IFNα-2a cytokine of claim 47 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

144. The modified IFNα-2a cytokine of claim 47 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

145. The modified IFNα-c cytokine of claim 49 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

146. The modified IFNα-c cytokine of claim 49 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

147. The modified IFNα-c cytokine of claim 49 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

148. The modified IFNα-2c cytokine of claim 51 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

149. The modified IFNα-2c cytokine of claim 51 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

150. The modified IFNα-2c cytokine of claim 51 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

151. The modified IFNα-1d cytokine of claim 53 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

152. The modified IFNα-1d cytokine of claim 53 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

153. The modified IFNα-1d cytokine of claim 53 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

154. The modified IFNα-5 cytokine of claim 55 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

155. The modified IFNα-5 cytokine of claim 55 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

156. The modified IFNα-5 cytokine of claim 55 that has increased biological activity compared to the unmodified cytokine, after incubation

with either mixtures of proteases, individual proteases, blood lysate or serum.

157. The modified IFNα-6 cytokine of claim 57 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

158. The modified IFNα-6 cytokine of claim 57 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

159. The modified IFNα-6 cytokine of claim 57 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

160. The modified IFNα-4 cytokine of claim 59 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

161. The modified IFNα-4 cytokine of claim 59 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

162. The modified IFNα-4 cytokine of claim 59 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

163. The modified IFNα-4b cytokine of claim 61 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

164. The modified IFNα-4b cytokine of claim 61 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

165. The modified IFNα-4b cytokine of claim 61 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

166. The modified IFNα-I cytokine of claim 63 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

167. The modified IFNα-I cytokine of claim 63 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

168. The modified IFNα-I cytokine of claim 63 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

169. The modified IFNα-J cytokine of claim 65 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

170. The modified IFNα-J cytokine of claim 65 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

171. The modified IFNα-J cytokine of claim 65 that has increased biological activity compared to the unmodified cytokine, after incubation

with either mixtures of proteases, individual proteases, blood lysate or serum.

172. The modified IFNα-H cytokine of claim 67 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

173. The modified IFNα-H cytokine of claim 67 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

174. The modified IFNα-H cytokine of claim 67 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

175. The modified IFNα-F cytokine of claim 69 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

176. The modified IFNα-F cytokine of claim 69 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

177. The modified IFNα-F cytokine of claim 69 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

178. The modified IFNα-8 cytokine of claim 71 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

179. The modified IFNα-8 cytokine of claim 71 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

180. The modified IFNα-8 cytokine of claim 71 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

181. The modified IFNα consensus cytokine of claim 73 that has increased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

182. The modified IFNα consensus cytokine of claim 73 that has decreased stability compared to any of the aligned cytokines, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

183. The modified IFNα consensus cytokine of claim 73 that has increased biological activity compared to any of the aligned cytokines, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

184. The modified IFNβ cytokine of claim 75 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

185. The modified IFNβ cytokine of claim 75 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

186. The modified IFNβ cytokine of claim 75 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

187. The modified IFN β-1 cytokine of claim 78 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

188. The modified IFN β-1 cytokine of claim 78 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

189. The modified IFN β-1 cytokine of claim 78 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

190. The modified IFN β-2a cytokine of claim 80 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

191. The modified IFN β-2a cytokine of claim 80 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

192. The modified IFN β-2a cytokine of claim 80 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

193. The modified IFN-gamma cytokine of claim 82 that has increased stability compared to the unmodified cytokine, wherein stability

is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

194. The modified IFN-gamma cytokine of claim 82 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

195. The modified IFN-gamma cytokine of claim 82 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

196. The modified IL-10 cytokine of claim 85 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

197. The modified IL-10 cytokine of claim 85 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

198. The modified IL-10 cytokine of claim 85 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

199. The modified erythropoietin cytokine of claim 88 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

200. The modified erythropoietin cytokine of claim 88 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

201. The modified erythropoietin cytokine of claim 88 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

202. The modified GM-CSF cytokine of claim 91 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

203. The modified GM-CSF cytokine of claim 91 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

204. The modified GM-CSF cytokine of claim 91 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

205. The modified Flt3 ligand cytokine of claim 94 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

206. The modified Flt3 ligand cytokine of claim 94 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

207. The modified Flt3 ligand cytokine of claim 94 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

208. The modified IL-2 cytokine of claim 97 that has increased stability compared to the unmodified cytokine, wherein stability is

assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

209. The modified IL-2 cytokine of claim 97 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

210. The modified IL-2 cytokine of claim 97 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

211. The modified IL-3 cytokine of claim 100 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

212. The modified IL-3 cytokine of claim 100 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

213. The modified IL-3 cytokine of claim 100 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

214. The modified SCF cytokine of claim 103 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

215. The modified SCF cytokine of claim 103 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

216. The modified SCF cytokine of claim 103 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

217. The modified IL-4 cytokine of claim 106 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

218. The modified IL-4 cytokine of claim 106 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

219. The modified IL-4 cytokine of claim 106 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

220. The modified IL-5 cytokine of claim 109 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

221. The modified IL-5 cytokine of claim 109 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

222. The modified IL-5 cytokine of claim 109 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

223. The modified IL-13 cytokine of claim 112 that has increased stability compared to the unmodified cytokine, wherein stability is

assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

224. The modified IL-13 cytokine of claim 112 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

225. The modified IL-13 cytokine of claim 112 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

226. The modified G-CSF cytokine of claim 115 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

227. The modified G-CSF cytokine of claim 115 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

228. The modified G-CSF cytokine of claim 115 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

229. The modified leptin cytokine of claim 118 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

230. The modified leptin cytokine of claim 118 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

231. The modified leptin cytokine of claim 118 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

232. The modified CNTF cytokine of claim 121 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

233. The modified CNTF cytokine of claim 121 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

234. The modified CNTF cytokine of claim 121 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

235. The modified LIF cytokine of claim 124 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

236. The modified LIF cytokine of claim 124 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

237. The modified LIF cytokine of claim 124 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

238. The modified oncostatin M cytokine of claim 127 that has increased stability compared to the unmodified cytokine, wherein stability

is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

239. The modified oncostatin M cytokine of claim 127 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

240. The modified oncostatin M cytokine of claim 127 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

241. The modified IL-12 cytokine of claim 130 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

242. The modified IL-12 cytokine of claim 130 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

243. The modified IL-12 cytokine of claim 130 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

244. The modified hGH of claim 133 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

245. The modified hGH of claim 133 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

246. The modified hGH of claim 133 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

247. The modified IL-6 cytokine of claim 136 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

248. The modified IL-6 cytokine of claim 136 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

249. The modified IL-6 cytokine of claim 136 that has increased biological activity compared to the unmodified cytokine, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

250. A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:

(a) identifying, within a target protein or peptide or plurality thereof, one or more target amino acids, wherein:

each target amino acid is designated an *in silico*-HIT (is-HIT); and

the is-HIT target amino acids are determined by identifying structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity;

(b) identifying one or more replacement amino acids, specific for each is-HIT, wherein each single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein contains a single amino acid replacement, and wherein each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the target protein or peptide;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array;

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such protein is designated a LEAD mutant protein;

251. The method of claim 250, wherein the predetermined property or activity of the evolved modified protein is increased resistance to proteolysis.

252. The method of claim 250, wherein the target proteins comprise a family.

253. The method of claim 250, wherein target proteins are cytokines.

254. The method of claim 253, wherein the cytokines are selected from the group consisting of interleukin-10 (IL-10), interferon beta (IFNβ), interferon alpha (IFNα), interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

255. The method of claim 250, wherein each candidate lead is individually prepared and screened to identify leads.

256. The method of claim 250, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids, or the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

257. The method of claim 250, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

258. The method of claim 250, further comprising:

(e) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(f) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(g) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified target protein and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

259. The method of claim 258, wherein the nucleic acid molecules in step (f) are generated by a method selected from among additive directional mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

260. The method of claim 250, wherein candidate leads are produced by replacing to a restricted subset of amino acids along the full length of a target protein.

261. The method of claim 250, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

262. The method of claim 250, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

263. The method of claim 258, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven,

eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

264. The method of claim 250, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified target protein.

265. The method of claim 250, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to the activity of the unmodified target protein.

266. The method of claim 250, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% compared to he activity of the unmodified target protein.

267. The method of claim 250, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater than the activity of the unmodified target protein.

268. The method of claim 250, wherein the replacing amino acids are selected using Percent Accepted Mutations (PAM) matrices.

269. The method of claim 250, wherein the replacing amino acids are pseudo-wild type amino acids.

270. The method of claim 250, wherein identification of the structurally homologous loci between the evolving target protein and a reference protein possessing the desired activity, comprises:

(a) comparing the 3-dimensional structures of the two or more proteins to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the evolving protein that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the reference protein.

271. The method of claim 270, wherein the comparison of the 3-dimensional structures of the evolving target protein and the reference protein is based upon their 3-dimensinal strucutures not upon alignment between their respective primary sequences.

272. The method of claim 270, wherein the evolving target protein and the reference protein belong to a family of sequence-related proteins.

273. The method of claim 270, wherein the evolving target protein and the reference protein belong respectively are non-related proteins or sequence-non-related proteins.

274. The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is in a region selected from the group consisting of:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

275. The method of claim 270, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and of the reference protein is determined by superposition and RMS deviation calculations using any combination of one or more of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA.

276. The method of claim 275, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA, when present.

277. The method of claim 275, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

278. The method of claim 275, wherein the degree of coincidence between the 3-dimensional structures of the evolving target protein and the reference protein is obtained using any combination of one or more of either Class Architecture, Topology and Homologous Superfamily (CATH); Combinatorial Extension of the optimal path (CE); Fold Classification based of Structure-Structure Alignment of Proteins (FSSP); Structural Classification of Proteins (SCOP); Vector Alignment Search Tool (VAST), and TOP.

279. A modified cytokine of claim 1 selected from the group consisting of modified cytokines comprising a sequence of amino acids set forth in any of SEQ ID Nos. 2-181, 233-1303 or a structural homolog thereof.

280. The modified cytokine of claim 279, selected from the group consisting of interleukin-10 (IL-10), interferon α, interferon β, interferon γ, granulocyte colony stimulating factor (G-CSF), leukemia inhibitory factor (LIF), human growth hormone (hGH), ciliary neurotrophic factor (CNTF), leptin, oncostatin M, interleukin-6 (IL-6) and interleukin-12 (IL-12), erythropoietin (EPO), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), Flt3 ligand and stem cell factor (SCF).

281. A method of generating a modified protein or cytokine having a pre-selected altered phenotype, comprising:

modifying a first protein or cytokine by a directed evolution method to produce an evolved protein or cytokine that has the altered phenotype to identify altered loci; and

comparing the structures of one or more members of the protein or cytokine family to identify structurally homologous loci for alteration;

altering the identified loci in members of the protein or cytokine family to produce proteins or cytokines that have the altered phenotype.

282. The method of claim 281, wherein directed evolution is effected by a rational directed evolution method.

283. The method of claim 281, wherein directed evolution is effected by a 2-dimensional rational scanning.

284. The method of claim 281, wherein identification of the structurally homologous loci between the evolved protein or cytokine and members of the protein or cytokine family, further comprises:

(a) comparing the 3-dimensional structures of the evolved protein or cytokine with one or more members of the protein or cytokine family to identify regions of high coincidence between their backbones, said regions designated as structurally homologous regions; and

(b) identifying is-HIT structurally homologous loci on the members of the protein or cytokine family that correspond to structurally related is-HIT amino acid positions within a structurally homologous region of the evolved protein or cytokine.

285. The method of claim 284, wherein the comparison of the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is made irrespective of any alignment between their respective sequences.

286. The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is in a region selected from the group consisting of:

(a) a small region on the two proteins;

(b) a large region on the two proteins; and

(c) a region that covers the full length of one or both of the proteins.

287. The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and of the evolved protein or cytokine is determined by superposition and RMS deviation calculations using any combination of

one or more of the peptide backbone atoms selected from the group consisting of: N, C, C(C=O), O and CA.

288. The method of claim 287, wherein the superposition and RMS deviation calculations are made using all of the peptide backbone atoms present selected from group the consisting of: N, C, C(C=O), O and CA.

289. The method of claim 287, wherein the superposition and RMS deviation calculations are carried out on a subset of regions or domains of a larger protein that adopts a structure similar to a smaller protein.

290. The method of claim 284, wherein the degree of coincidence between the 3-dimensional structures of the members of the protein or cytokine family and the evolved protein or cytokine is obtained using any combination of one or more of either CATH (Class Architecture, Topology and Homologous Superfamily); CE (Combinatorial Extension of the optimal path); FSSP (Fold Classification based of Structure-Structure Alignment of Proteins); SCOP (Structural Classification of Proteins); VAST (Vector Alignment Search Tool), and TOP.

291. The method of claim 283, wherein the 2-dimensional rational scanning method comprises:

(a) identifying, within the first protein or cytokine, one or more target amino acids amenable to providing the altered phenotype upon amino acid replacement, wherein each target amino acid is designated an *in silico*-HIT (is-HIT);

(b) identifying one or more replacement amino acids, specific for each is-HIT, amenable to providing the altered phenotype upon amino acid replacement, wherein each single amino acid replacement within the protein or cytokine is designated as a candidate LEAD protein;

(c) producing a population of sets of nucleic acid molecules that encode each of the candidate LEAD proteins, wherein each candidate LEAD protein comprises a single amino acid replacement, and wherein

each polynucleotide in a set encodes a candidate LEAD protein that differs by one amino acid from the unmodified protein or cytokine;

(d) introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are present in an addressable array;

(e) individually screening the sets of encoded candidate LEAD proteins to identify one or more candidate LEAD proteins that has activity that differs from the unmodified protein or cytokine, wherein each such protein is designated a LEAD mutant protein.

292. The method of claim 291, wherein the array comprises a solid support with wells; and each well contains one set of cells.

293. The method of claim 291, wherein the nucleic acid molecules comprise plasmids; and the cells are eukaryotic cells that are transfected with the plasmids.

294. The method of claim 291, wherein the nucleic acid molecules comprise plasmids and the cells are bacterial cells.

295. The method of claim 291, wherein the nucleic acid molecules in step (c) are produced by site-specific mutagenesis.

296. The method of claim 291, further comprising:

(f) generating a population of sets of nucleic acid molecules encoding a set of candidate super-LEAD proteins, wherein each candidate super-LEAD protein comprises a combination of two or more of the single amino acid mutations derived from two or more LEAD mutant proteins;

(g) introducing each set of nucleic acid molecules encoding candidate super-LEADs into cells and expressing the encoded candidate super-LEAD proteins; and

(h) individually screening the sets of encoded candidate super-LEAD proteins to identify one or more proteins that has activity that differs from the unmodified protein or cytokine and has properties that differ from the original LEADs, wherein each such protein is designated a super-LEAD.

297. The method of claim 296, wherein the nucleic acid molecules in step (f) are produced by a method selected from among Additive Directional Mutagenesis (ADM), multi-overlapped primer extensions, oligonucleotide-mediated mutagenesis, nucleic acid shuffling, recombination, site-specific mutagenesis, and *de novo* synthesis.

298. The method of claim 291, wherein the is-HITs identified in step (a) correspond to a restricted subset of amino acids along the full length target protein.

299. The method of claim 291, wherein the replacement amino acids identified in step (b) correspond to a restricted subset of the 19 remaining non-native amino acids.

300. The method of claim 291, wherein the nucleic acids of step (c) are produced by systematically replacing each codon that is an is-HIT, with one or more codons encoding a restricted subset of the remaining amino acids, to produce nucleic acid molecules each differing by at least one codon and encoding candidate LEADs.

301. The method of claim 296, wherein the number of LEAD amino acid positions generated on a single nucleic acid molecule is selected from the group consisting of: two, three, four, five, six, seven, eight, nine, ten or more LEAD amino acid positions up to all of the LEAD amino acid positions.

302. The method of claim 291, wherein the LEADs or super-LEADs possess increased resistance to proteolysis compared to unmodified protein or cytokine.

303. The method of claim 291, wherein the change in activity is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100% of the activity of the unmodified target protein.

304. The method of claim 291, wherein the change in activity is not more than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, of the activity of the unmodified target protein.

305. The method of claim 291, wherein the change in activity is at least about 2 times, 3 times, 4 times, 5 times, 6 times, 7 times, 8 times, 9 times, 10 times, 20 times, 30 times, 40 times, 50 times, 60 times, 70 times, 80 times, 90 times, 100 times, 200 times, 300 times, 400 times, 500 times, 600 times, 700 times, 800 times, 900 times, 1000 times, or more greater or less than the activity of the unmodified target protein.

306. A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFN-2c cytokine selected from the group consisting of proteins comprising one or more single amino acid replacements corresponding to the replacement of: N by D at position 45; D by G at position 94; G by R at position 102; A by G at position 139; or any combination thereof.

307. A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFN-2c cytokine selected from selected from the group consisting of proteins comprising one or more single amino acid replacements in any of SEQ ID Nos. 1, 182, 185 or 232 or any combination thereof corresponding to the replacement: L by V at position 3; L by I at position 3; P by S at position 4; P by by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at

position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; and E by H at position 165 or any combination thereof, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID NOS:1 or 182.

308. A modified cytokine of claim 1 that is an IFNα-2b, IFNα-2a, IFN-2c cytokine selected from selected from the group consisting of proteins comprising one or more single amino acid replacements in any of SEQ ID Nos. 1, 182, 185 or 232 or any combination thereof corresponding to the replacement L by V at position 3; L by I at position 3; P by S at position 4; P by A at position 4; R by H at position 12; R by Q at position 12; R by H at position 13; R by Q at position 13; M by V at position 16; M by I at position 16; R by H at position 22; R by Q at position 22; R or K by H at position 23; R or K by Q at position 23; F by I at position 27; F by V at position 27; L by V at position 30; L by I at position 30; K by Q at position 31; K by T at position 31; R by H at position 33; R by Q at position 33; E by Q at position 41; E by H at position 41; K by Q at position 49; K by T at position 49; E by Q at position 58; E by H at position 58; K by Q at position 70; K by T at position 70; E by Q at position 78; E by H at position 78; K by Q at

position 83; K by T at position 83; Y by H at position 89; Y by I at position 89; E by Q at position 96; E by H at position 96; E by Q at position 107; E by H at position 107; P by S at position 109; P by A at position 109; L by V at position 110; L by I at position 110; M by V at position 111; M by I at position 111; E by Q at position 113; E by H at position 113; L by V at position 117; L by I at position 117; R by H at position 120; R by Q at position 120; K by Q at position 121; K by T at position 121; R by H at position 125; R by Q at position 125; L by V at position 128; L by I at position 128; K by Q at position 131; K by T at position 131; E by Q at position 132; E by H at position 132; K by Q at position 133; K by T at position 133; K by Q at position 134; K by T at position 134; Y by H at position 135; Y by I at position 135; P by S at position 137; P by A at position 137; M by V at position 148; M by I at position 148; R by H at position 149; R by Q at position 149; E by Q at position 159; E by H at position 159; L by V at position 161; L by I at position 161; R by H at position 162; R by Q at position 162; K by Q at position 164; K by T at position 164; E by Q at position 165; E by H at position 165; N by D at position 45; D by G at position 94; G by R at position 102; and A by G at position 139, wherein residue 1 corresponds to residue 1 of the mature IFNα-2b or IFNα-2a cytokine set forth in SEQ ID No. 1 or 182.

309. The modified cytokine of claim 1, that is an interferon β (IFNβ).

310. A modified IFN β cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:196, corresponding to the replacement of M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at

position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at

position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at

position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at

position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID NO:196.

311. A modified cytokine of claim 1 that comprises one or more pseudo-wild type mutations.

312. The modified cytokine of claim 311 that is a modified IFNβ.

313. A modified IFNβ cytokine of claim 309 that has increased antiviral activity compared to the unmodified cytokine.

314. The modified IFNβ cytokine of claim 313, wherein antiviral activity is assessed by measuring replication by reverse transcription quantification PCR (RT-qPCR) or CPE (cythopathic effect).

315. A modified IFNα-2b or IFNα-2a cytokine of claim 309 that has more antiviral activity than antiproliferative activity compared to the unmodified cytokine.

316. The cytokine of claim 315, wherein antiproliferative activity is assessed by measuring cell proliferation in the presence of the cytokine.

317. A modified IFNβ cytokine of claim 309 that binds to an IFN receptor, but exhibits when compared to unmodified IFNβ, decreased antiviral activity and decreased antiproliferative activity relative to its receptor binding activity.

318. A modified cytokine of claim 1, comprising two or more mutations.

319. A pharmaceutical composition, comprising a cytokine of claim 1 in a pharmaceutically acceptable carrier.

320. A modified cytokine that exhibits greater resistance to proteolysis compared to the unmodified cytokine, comprising one or more amino acid replacements at one or more target positions on the cytokine corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of the IFNβ modified cytokines of claim 309.

321. A modified cytokine of claim 320, wherein the resistance to proteolysis is measured by mixing it with a protease in vitro, incubation with blood or incubation with serum.

322. A cytokine structural homolog of an IFNβ modified cytokine of claim 309, comprising one or more amino acid replacements in the cytokine structural homolog at positions corresponding to the 3-dimensional-structurally-similar modified positions within the 3-D structure of the modified IFNβ.

323. A cytokine homolog of claim 322, wherein the homolog has increased resistance to proteolysis compared to its unmodified cytokine counterpart, wherein the resistance to proteolysis is measured by mixture with a protease *in vitro*, incubation with blood, or incubation with serum.

324. A modified IFNβ cytokine, comprising one or more amino acid replacements at one or more target positions in SEQ ID NO. 196 in the IFNβ corresponding to a structurally-related modified amino acid position within the 3-dimensional structure of IFNβ modified cytokines of claim 309, wherein the replacements lead to greater resistance to proteases, as assessed by incubation with a protease or a with a blood lysate or by incubation with serum, compared to the unmodified IFNβ.

325. The modified IFNβ cytokine of claim 309 that has increased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication or to stimulate cell proliferation in appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

326. The modified IFNβ cytokine of claim 309 that has decreased stability compared to the unmodified cytokine, wherein stability is assessed by measuring residual biological activity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

327. The modified IFNβ cytokine of claim 309 that has increased biological activity compared to the unmodified cytokine, wherein activity is assessed by measuring the capacity to either inhibit viral replication in the appropriate cells or to stimulate cell proliferation of the appropriate cells, after incubation with either mixtures of proteases, individual proteases, blood lysate or serum.

328. A modified of IFNβ cytokine of claim 309, selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:196, or any combination thereof, corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q

at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at

position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at

position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at

position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90,

wherein residue 1 corresponds to residue 1 of the mature IFNβ cytokine set forth in SEQ ID NOS:196.

329. A modified IFNβ cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:196, or any combination thereof, corresponding to the replacement of: D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at

position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

330. A modified IFNβ cytokine of claim 309 selected from the group consisting of proteins comprising one or more single amino acid replacements in SEQ ID NOS:196, or any combination thereof,

corresponding to the replacement of: M by V at position 1, M by I at position 1, M by T at position 1, M by Q at position 1, M by A at position 1, L by V at position 5, L by I at position 5, L by T at position 5, L by Q at position 5, L by H at position 5, L by A at position 5, F by I at position 8, F by V at position 8, L by V at position 9, L by I at position 9, L by T at position 9, L by Q at position 9, L by H at position 9, L by A at position 9, R by H at position 11, R by Q at position 11, F by I at position 15, F by V at position 15, K by Q at position 19, K by T at position 19, K by S at position 19, K by H at position 19, W by S at position 22, W by H at position 22, N by H at position 25, N by S at position 25, N by Q at position 25, R by H position 27, R by Q position 27, L by V at position 28, L by I at position 28, L by T at position 28, L by Q at position 28, L by H at position 28, L by A at position 28, E by Q at position 29, E by H at position 29, Y by H at position 30, Y by I at position 30, L by V at position 32, L by I at position 32, L by T at position 32, L by Q at position 32, L by H at position 32, L by A at position 32, K by Q at position 33, K by T at position 33, K by S at position 33, K by H at position 33, R by H at position 35, R by Q at position 35, M by V at position 36, M by I at position 36, M by T at position 36, M by Q at position 36, M by A at position 36, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by, Q at position 47, L by H at position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by Q at position 73, D by H at position 73, D by G at position 73, E by Q at position 81, E by H at position 81, E by Q at position 85, E by H at position 85, Y by H at position 92, Y by I at position 92, K by Q at position 99, K by T at position 99, K by S at

position 99, K by H at position 99, E by Q at position 103, E by H at position 103, E by Q at position 104, E by H at position 104, K by Q at position 105, K by T at position 105, K by S at position 105, K by H at position 105, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 138, Y by I at position 138, R by H at position 152, R by Q at position 152, Y by H at position 155, Y by I at position 155, R by H at position 159, R by Q at position 159, Y by H at position 163, Y by I at position 163, R by H at position 165, R by Q at position 165, M by D at position 1, M by E at position 1, M by K at position 1, M by N at position 1, M by R at position 1, M by S at position 1, L by D at position 5, L by E at position 5, L by K at position 5, L by N at position 5, L by R at position 5, L by S at position 5, L by D at position 6, L by E at position 6, L by K at position 6, L by N at position 6, L by R at position 6, L by S at position 6, L by Q at position 6, L by T at position 6, F by E at position 8, F by K at position 8, F by R at position 8, F by D

at position 8, L by D at position 9, L by E at position 9, L by K at position 9, L by N at position 9, L by R at position 9, L by S at position 9, Q by D at position 10, Q by E at position 10, Q by K at position 10, Q by N at position 10, Q by R at position 10, Q by S at position 10, Q by T at position 10, S by D at position 12, S by E at position 12, S by K at position 12, S by R at position 12, S by D at position 13, S by E at position 13, S by K at position 13, S by R at position 13, S by N at position 13, S by Q at position 13, S by T at position 13, N by D at position 14, N by E at position 14, N by K at position 14, N by Q at position 14, N by R at position 14, N by S at position 14, N by T at position 14, F by D at position 15, F by E at position 15, F by K at position 15, F by R at position 15, Q by D at position 16, Q by E at position 16, Q by K at position 16, Q by N at position 16, Q by R at position 16, Q by S at position 16, Q by T at position 16, C by D at position 17, C by E at position 17, C by K at position 17, C by N at position 17, C by Q at position 17, C by R at position 17, C by S at position 17, C by T at position 17, L by N at position 20, L by Q at position 20, L by R at position 20, L by S at position 20, L by T at position 20, L by D at position 20, L by E at position 20, L by K at position 20, W by D at position 22, W by E at position 22, W by K at position 22, W by R at position 22, Q by D at position 23, Q by E at position 23, Q by K at position 23, Q by R at position 23, L by D at position 24, L by E at position 24, L by K at position 24, L by R at position 24, W by D at position 79, W by E at position 79, W by K at position 79, W by R at position 79, N by D at position 80, N by E at position 80, N by K at position 80, N by R at position 80, T by D at position 82, T by E at position 82, T by K at position 82, T by R at position 82, I by D at position 83, I by E at position 83, I by K at position 83, I by R at position 83, I by N at position 83, I by Q at position 83, I by S at position 83, I by T at position 83, N by D at position 86, N by E at position 86, N by K at position 86, N by R at position 86, N by Q at

position 86, N by S at position 86, N by T at position 86, L by D at position 87, L by E at position 87, L by K at position 87, L by R at position 87, L by N at position 87, L by Q at position 87, L by S at position 87, L by T at position 87, A by D at position 89, A by E at position 89, A by K at position 89, A by R at position 89, N by D at position 90, N by E at position 90, N by K at position 90, N by Q at position 90, N by R at position 90, N by S at position 90, N by T at position 90, V by D at position 91, V by E at position 91, V by K at position 91, V by N at position 91, V by Q at position 91, V by R at position 91, V by S at position 91, V by T at position 91, Q by D at position 94, Q by E at position 94, Q by Q at position 94, Q by N at position 94, Q by R at position 94, Q by S at position 94, Q by T at position 94, I by D at position 95, I by E at position 95, I by K at position 95, I by N at position 95, I by Q at position 95, I by R at position 95, I by S at position 95, I by T at position 95, H by D at position 97, H by E at position 97, H by K at position 97, H by N at position 97, H by Q at position 97, H by R at position 97, H by S at position 97, H by T at position 97, L by D at position 98, L by E at position 98, L by K at position 98, L by N at position 98, L by Q at position 98, L by R at position 98, L by S at position 98, L by T at position 98, V by D at position 101, V by E at position 101, V by K at position 101, V by N at position 101, V by Q at position 101, V by R at position 101, V by S at position 101, V by T at position 101, M by C at position 1, L by C at position 6, Q by C at position 10, S by C at position 13, Q by C at position 16, L by C at position 17, V by C at position 101, L by C at position 98, H by C at position 97, Q by C at position 94, V by C at position 91, N by C at position 90, D by Q at position 39, D by H at position 39, D by G at position 39, E by Q at position 42, E by H at position 42, K by Q at position 45, K by T at position 45, K by S at position 45, K by H at position 45, L by V at position 47, L by I at position 47, L by T at position 47, L by Q at position 47, L by H at

position 47, L by A at position 47, K by Q at position 52, K by T at position 52, K by S at position 52, K by H at position 52, F by I at position 67, F by V at position 67, R by H at position 71, R by Q at position 71, D by H at position 73, D by G at position 73, D by Q at position 73, E by Q at position 81, E by H at position 81, E by Q at position 107, E by H at position 107, K by Q at position 108, K by T at position 108, K by S at position 108, K by H at position 108, E by Q at position 109, E by H at position 109, D by Q at position 110, D by H at position 110, D by G at position 110, F by I at position 111, F by V at position 111, R by H at position 113, R by Q at position 113, L by V at position 116, L by I at position 116, L by T at position 116, L by Q at position 116, L by H at position 116, L by A at position 116, L by V at position 120, L by I at position 120, L by T at position 120, L by Q at position 120, L by H at position 120, L by A at position 120, K by Q at position 123, K by T at position 123, K by S at position 123, K by H at position 123, R by H at position 124,, R by Q at position 124, R by H at position 128, R by Q at position 128, L by V at position 130, L by I at position 130, L by T at position 130, L by Q at position 130, L by H at position 130, L by A at position 130, K by Q at position 134, K by T at position 134, K by S at position 134, K by H at position 134, K by Q at position 136, K by T at position 136, K by S at position 136,, K by H at position 136, E by Q at position 137, E by H at position 137, Y by H at position 163, Y by I at position 163I, R by H at position 165, R by Q at position 165, wherein the first amino acid listed is substituted by the second at the position indicated.

331. A modified IFNβ of claim 330 selected from the group consisting of a modified IFNβ set forth in any of SEQ ID Nos.234-289, 989-1302.